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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/909,005	07/18/2001	Henry Yue	PF-0599-2 DIV	9313

27904 7590 06/20/2002

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/20/2002 7

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/909,005	Applicant(s) YUE ET AL.	
	Examiner Maher M. Haddad	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8 July 2001 and 3-25-02*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,9,10 and 29-45* is/are pending in the application.

4a) Of the above claim(s) *1, 2, 9, 29, 32, 34, 43 and 44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10, 30, 31, 33, 35-42* is/are rejected.

7)☒ Claim(s) *45* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3*
4) ☐ Interview Summary (PTO-413) Paper No(s) _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other

DETAILED ACTION

1. Claims 1, 2, 9, 10 and 29-45 are pending.

Upon reconsideration Examiner has rejoined Groups V and VI to elected Group II which read on an antibody that specifically binds to polypeptide of SEQ ID NO: 1 and method of preparing a polyclonal antibody (claim 35) and a method of making a monoclonal antibody (claim 38).

2. Applicant's election with traverse of Group II, claims 10, 30-31, 33, 36, 37, 39-42 and 45, (now claims10, 30-31, 33, 35-42 and 45) drawn to an antibody which specifically binds to a polypeptide of SEQ IN NO. 1 and a method of making filed on 3-25-02, is acknowledged.

Applicant's traveral is on the grounds that the invention encompassed by the claims of Group II could be examined at the same time as the inventions encompassed by the claims of Groups III-IV and VII-VIII and a search of the prior art to determine the novelty of the antibody of the invention would provide information regarding the novelty of the polypeptide. This is not found persuasive because Groups II-IV and VII-VIII are classified in different Classes and are recognized divergent subject matter. Specifically, the a diagnostics test of Group III recites *in vitro* conditions associated with CJPDZ while the method of diagnosing of Group IV recites *in vivo* condition associated with CJPDZ and the method of detecting the polypeptide of Group VII recites in vitro binding of the antibodies and the polypeptide. The antibody in Group II and the methods of diagnosing, detecting and purifying have different classification which require a different search. Therefore, the methods and antibodies recited are distinct and independent, and searches of all groups would place an undue burden upon the examiner due to the distinct and separate classification of each Group.

The requirement is still deemed proper and is therefore made final.

3. Claims 1, 2, 9, 29, 32, 34, 43 and 44 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 10, 30-31, 33, 35-42 and 45 are under examination as they read on an antibody which specifically binds to a polypeptide of SEQ IN NO: 1 and methods of making.

5. The specification on page 1 should be amended to reflect the status of 09/370,102.

6. Claims 10, 30-31, 33, 35-42 and 45 are objected to in that they are dependent on non-elected claims 1 and 2 and should be written as independent claims.

7. Applicant's IDS, filed 7-18-01 (Paper No. 3), is acknowledged. However, the references were crossed out as the entire documents were not found. Applicant is invited to produce such documents.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 33 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 33 has no antecedent basis in base claim 31, because claim 31 recites a composition comprising an antibody per se, whereas a labeled antibody is recited in claim 33.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 10, 30, 31, 33, and 35-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody which specifically binds to a polypeptide of SEQ ID NO:1 for a diagnostic assay, does not reasonably provide enablement for any antibody which specifically binds to any polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:1; any antibody which specifically binds to any biologically active fragment of a polypeptide of SEQ ID NO1; or any antibody which specifically binds to an immunogenic fragment of a polypeptide of SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There is insufficient guidance and direction as to how to make and use the claimed antibodies, wherein the antibodies which specifically binds to any polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:1; for any antibody to a biologically active fragment of a polypeptide of SEQ ID NO1; or any antibody to a immunogenic fragment of a polypeptide of SEQ ID NO:1.

The present specification fails to provide sufficient disclosure of amino acid fragments that have the biological activity of SEQ ID NO:1; immunogenic fragments of SEQ ID NO:1, or a polypeptide at least 90% sequence identity to the sequence of SEQ ID

sufficient guidance as to which of the amino acids may be changed while the biological activity is retained. In addition, the term "comprising" in non-elected base claim 1b is open-ended, it expand the "naturally occurring polypeptide" to include additional non disclosed amino acids.

Colman *et al* in Research in Immunology (145(1):33-36, 1994) teach single amino acid changes in an antigen can effectively abolish antibody antigen binding. Abaza *et al* in Journal of Protein Chemistry (11(5):433-444, 1992) teach that single amino acid substitutions outside the antigenic site on a protein effect antibody binding. Further, Lederman *et al* in Molecular Immunology (28:1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). Additionally, Li *et al* in PNAS (77:3211-3214, 1980) disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document).

Because of the unpredictability and the lack of guidance, an undue experimentation would be required to determine which modifications would be acceptable to retain occluding structural and functional activity, and the fact that the relationship between the sequence of a protein/peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g. see Ngo *et al* in the Protein Folding problem and Tertiary Structure prediction, 1994, Merz *et al*., (ed), Birkhauser, Boston, MA, pp.433 and 492-495), it would require an undue amount of experimentation for one of skill in the art to arrive at the *biologically active* fragments, *immunogenic fragments* or *a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:1* encompassed by the claimed invention.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

10. Claims 10, 30, 31, 33, and 35-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of an antibody which specifically binds to a polypeptide of SEQ ID NO:1; however, applicant is not in possession of any antibody which specifically binds to any polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:1; any antibody which specifically binds to any biologically active fragment of a polypeptide of SEQ ID NO1; or any antibody which specifically binds to an immunogenic fragment of a polypeptide of SEQ ID NO:1. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 10, 31, 33, 35-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent. No. 6,051,374 in view of U.S. Patent No. 6,210,675.

The '374 patent teaches a 5 amino acid immunogenic fragment of the claimed SEQ ID NO:1 (see sequence alignment in particular).

The claimed invention differs from the reference teachings only by the recitation of an antibody which specifically binds to an immunogenic fragment in claims 10, 36, 39 and 41-42; a composition comprising an antibody and an acceptable excipient in claims 31, 37 and 40; a composition wherein the antibody is labeled in claim 33; a method of preparing a polyclonal antibody in claim 35; a method of making a monoclonal antibody in claim 38.

The '675 patent teaches that an antigenic fragment of an antigen having a minimum of five amino acids and each fragment is usually coupled to some carrier molecule to facilitate the induction of an immune response (column 2, lines 41-65 and column 3, lines 1-5 in particular). Furthermore, the '675 patent teaches antibodies and methods of producing polyclonal and monoclonal antibodies to a polypeptide (column 5, lines 5-47). Polyclonal antibodies against a polypeptide can be obtained by injecting a polypeptide, into a mammalian host such as a mouse, rat, sheep or rabbit and recovering the antibody thus produced; plasma samples being taken at appropriate intervals are assay for the antibody specificity. Monoclonal antibodies against a polypeptide can be obtained by fusing cells of an immortalizing cell line with cells which produce antibody against the polypeptide, and culturing the fused immortalized cell line. Also, the '675 patent teaches that antibodies produced can be used in quality control testing of the polypeptide; purification of the polypeptide or lysate; epitope mapping, when labeled, as a conjugate in a competitive type assay; and for antibody detection (column 5, lines 6-13 in particular). Finally, the '675 patent teaches that the antibody is in solution (column 7, lines 58-62 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the peptide taught by the '374 patent to make monoclonal and polyclonal antibodies as taught by '675 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the antigenic fragment would facilitate the induction of an immune response to produce antibodies and the antibodies produced can be used in quality control testing of the polypeptide, purification of the polypeptide or lysate, epitope mapping and for antibody detection as taught by the '675 patent.

Claims 41-42 are included because an antibody is the same antibody irrespective of how it is made.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. Claims 10 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent. No. 6,051,374 in view of U.S. Patent No. 6,210,675, and further in view of Owens *et al* (1994).

The teachings of '374 patent and the '675 patent have been discussed, supra.

The claimed invention differs from the combined reference teachings only by the recitation of a chimeric antibody, a single chain antibody, a Fab fragment, a $F(ab')_2$ fragment or a humanized antibody.

Owens *et al* teach the modification of murine antibodies such as a chimeric antibody, a single chain antibody, a Fab fragment, a $F(ab')_2$ fragment or a humanized antibody antibodies monoclonal antibody technology, chimeric, single chain, Fab fragments, and $F(ab')_2$. Owens *et al* further teach humanized antibodies use in therapy of human diseases or disorders, since the human or humanized antibodies are much less likely to induce an immune response. Also, antibody fragments are the reagents of choice for some clinical applications, and the chimeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement – dependent cytotoxcity (see the entire document).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the immunogenic fragment taught by '374 patent to produce the antibody taught by the '675 patent as chimeric, humanized antibody, Fab and $F(ab')_2$ fragments taught by the Owens *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the humanized antibodies are much less likely to induce an immune response and because the antibody fragments are the reagents of choice for some clinical applications and the chimaeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement-dependent cytotoxcity as taught by Owens *et al*.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claims 10 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent. No. 6,051,374 in view of U.S. Patent No. 6,210,675, and further in view of Bird *et al* (1988).

The teachings of '374 patent and the '675 patent have been discussed, supra.

The claimed invention differs from the combined reference teachings only by the recitation of a single chain antibody.

Bird *et al* teach a single chain antigen binding proteins composed of an antibody variable light – chain amino acid sequence (V_L) tethered to a variable heavy –chain sequence (V_H) by a designed peptide that links the carboxyle terminus of the V_L sequence to the amino terminus of the V_H sequence. Bird *et al* further teach that the single chain antibodies have significant advantages over monoclonal antibodies in a number of applications such as lower back ground in imaging applications since the single chain antibody lack the Fc portion (see the entire document and page 426, left column, 2nd paragraph in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the immunogenic fragment taught by the '374 patent to produce the antibody taught by the '675 patent as a single chain antibody as taught by the Bird *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because single chain antibodies have significant advantages over monoclonal antibodies in a number of applications such as lower back ground in imaging applications since the single chain antibody lack the Fc portion as taught by Bird *et al*.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. Claim 45 is objected to as being dependent upon a non elected base claim 2, but would be allowable if rewritten in independent form including all of the limitations of the base claim.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the

examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
June 17, 2002

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